Three-dimensional and Power Doppler Ultrasonography in Infertility and Reproductive Endocrinology

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SUMMARY

Three-dimensional (3D) ultrasound is an easy and noninvasive technique in the clinical practice of obstetrics and gynecology. It can be used in the analysis of morphologic anatomy and volume measurement and is highly reproducible. Power Doppler ultrasound can further depict and quantify the microcirculation of the target organ or the region of interest. The aim of this review is to report the present status and the development of 3D ultrasonography, as well as 3D power Doppler in the field of infertility and reproductive endocrinology. 3D ultrasound may help us investigate the functional and potential roles in various pathologic conditions of the female pelvis. Furthermore, 3D ultrasound may also provide substantial assistance in the clinical application of infertility and reproductive endocrinology. [*Taiwan J Obstet Gynecol* 2007;46(3):209–214]

Key Words: endometriosis, menopause, müllerian duct anomaly, ovulation induction, polycystic ovary syndrome, three-dimensional ultrasound

Introduction

Conventional two-dimensional (2D) ultrasound is a valuable diagnostic tool in the field of obstetrics and gynecology. Nevertheless, three-dimensional (3D) ultrasound and rendering mode can illustrate even more sophisticated imaging with nearly real-time computerized reconstruction. With the recent advent of 3D sonography, prenatal diagnosis of fetal malformations can be achieved accurately [1]. In addition, 3D ultrasound can help in differentiating different uterine malformations and intrauterine pathologic lesions [2–6]. Once the volumes are scanned and stored digitally, the images that may be missed easily or visualized incompletely on conventional 2D sonography can be clearly depicted on 3D ultrasound without torsion or being missed. In 3D ultrasound, three perpendicular planes displayed on the screen can be rotated and adjusted simultaneously into a more suitable anatomic orientation obtained from any arbitrary planes. Optimal display of stored volume data by rotation can also provide more detailed morphology for accurate diagnosis.

To date, various imaging modes are available in the processing of 3D imaging. A combination of suitable modes allows us to visualize the structures of the target organs. In other words, 3D volumetry may be indicated in the measurement of tumors or any organs of interest [7–9]. Besides, conventional 2D color Doppler flow mapping is less sensitive to small vessels and/or slow flow in detecting vascularity. However, color amplitude imaging (power Doppler) can provide information on the quality and quantity of moving blood cells per volume to demonstrate the underlying vascularity of the target organ. 3D power Doppler ultrasonography is more accurate than 2D imaging in quantifying the blood flow and vascularization of the ovarian stroma [10]. Moreover, current development of 3D power Doppler ultrasound has been proved to be beneficial in the

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diagnosis and evaluation of infertility and reproductive endocrinology [11–15]. Therefore, the aim of this review is to reanalyze and reassess the recent update of clinical applications in this field by 3D and power Doppler ultrasound.

Polycystic Ovary Syndrome (PCOS)

The imaging of 3D ultrasound demonstrates two traditional planes and a reconstructed third dimensional plane, which may help to visualize any anatomic changes in size, location and characteristics of the ovaries and uterus. Transabdominal or transvaginal 3D ultrasound not only facilitates noninvasive evaluation and volume calculation but also completes the examination in a short time without making patient discomfort. The ovaries can usually be visualized by transvaginal ultrasound easily. 3D ultrasound can further localize the largest dimension of ovaries in the three planes through rotation of the stored images. Sometimes, in spite of the identification of hypogastric vessels, it is difficult to localize the ovaries because of their small sizes with no obvious follicles. Detailed search after the documentation of target box of scanning with 3D ultrasound may assist in localizing the ovaries.

PCOS is a common cause of ovarian dysfunction. In our study of 3D volumetry, the ovaries of PCOS patients were larger in size, area, and volume than those of normal controls [7]. Using 3D ultrasound, the stroma and volume (trapezoid formula) determinations can be evaluated more accurately than those of traditional 2D ultrasonography (ellipsoid formula: height $\times$ width $\times$ thickness $\times$ 0.523). The mean ovarian volume using 3D transvaginal ultrasound was $11.3 \pm 3.5\,cm^3$ in PCOS patients and $5.5 \pm 1.4\,cm^3$ in control group. The diagnostic cutoff values of ovarian area, stroma, and volume in PCOS were $5.2\,cm^2$, $4.6\,cm^2$, and $6.6\,cm^3$ with high sensitivity and specificity, respectively. After laparoscopic ovarian drilling, the ovarian volume showed a significant change from $12.52\,cm^3$ to $10.97\,cm^3$ in our 3D transabdominal study, but there was no significant change in uterine volumes [16]. This finding demonstrates that ovarian drilling might restore the ovarian endocrine profile and sizes without affecting the uterus.

Notably, 3D power Doppler ultrasound can provide additional information on the quantity of moving blood cells per volume and is sensitive for demonstrating the real vascularity of the target organ. We have observed that the intraobserver and interobserver variabilities of 3D power Doppler were acceptable with high reproducibility at the ultrasound laboratory of our department, indicating that 3D power Doppler angiography can be used in clinical practice and research.

To date, several parameters of the color histogram using 3D power Doppler ultrasonography are commonly used to quantify the blood flow and vascularization of the ovarian stroma, including mean gray value, vascularization index (VI; an estimation of vessel density, determined by the formula: color voxels/[total voxels – background voxels]), flow index (FI; the average intensity of the flow, determined by the formula: weighted color voxels/[color voxels – border voxels]), and vascularization flow index (VFI; both flow and vessel intensity, determined by the formula: weighted color vexels/[total voxels – background voxels]). Using the virtual organ computer-aided analysis software for histogram analysis, these parameters are calculated after the total volume of the target organ has been stored, retrieved and assessed.

For the study of PCOS, the setting condition for our 3D power Doppler transvaginal ultrasound (7.5 MHz, Voluson 530D; Medison-Kretz, Seoul-Zipf, Korea-Austria) was as follows: angio mode, cent; FRQ, mid; frame filter, 3; line density, 254; enhance, 3; far gain, max 62; persist 0.3/0.4; quality, 12; density, 6; balance, G > 192; reject, 79; actual power, 2dB; and pulse repetition frequency, 1.0. In our study, 3D transvaginal power Doppler ultrasound demonstrated increased VI, FI and VFI in the ovarian stromal Doppler signals in PCOS assessed on day 2 or 3 of the menstrual cycle [10]. This result might imply the excessive response often observed during gonadotrophin administration in women with PCOS, and the ovarian stromal signal of 3D power Doppler ultrasound may be a new parameter to assist in the ultrasound diagnosis of PCOS. In addition, slight differences in PCOS parameters in intraovarian stroma only demonstrated significantly decreased VI and VFI by 3D transabdominal power Doppler after operative treatment in our study. Treatment using laparoscopic ovarian drilling in young adult women with PCOS did not influence leptin levels; rather, it changed the ovarian stromal blood flow dynamics in a short-term follow-up. From our study, the surgical procedure may be beneficial to both endocrine profiles and intraovarian stromal flow in PCOS patients.

In the study of young PCOS female patients, we used 3D transabdominal 5.0 MHz power Doppler ultrasound scanner (Voluson 530D, Medison-Kretz, Seoul-Zipf, Korea-Austria; setting condition: CFM-PRF 1.0, C-PWR 5dB, angio mode, cent; FRQ, low; persist, 0.3/0.4; quality, 9; density, 8; enhance, 3; balance, G > 192; reject, 81), because there was no history of sexual exposure [16]. The decreased power Doppler signal may be due to different settings between transabdominal and transvaginal power Doppler ultrasound. In addition, the attenuation effect is more obvious in transabdominal scanning because of the well-distended bladder that may play a role in the lower values of flow indices and also of the attenuation problem of the ultrasound signal with increasing distance from the transducer. However, sophisticated experience is still needed when using 3D power Doppler ultrasound, such as choosing the best view of the target organ, and many technical problems, such as diminishing attenuation effect and optimizing the setting conditions, need to be further resolved [17].

In 2003, the Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group defined the ultrasound criteria as the presence of at least twelve follicles in each ovary, which are measured between 2–9 mm in diameter, and/or increased ovarian volume (more than 10 mL) [18]. It serves as an important guideline in the ultrasound diagnosis of PCOS. However, there is no mention of the characteristics of ovarian stroma and the distribution of follicles. Their formula for ovarian volume calculation is based on 2D (ellipsoid) measurement, which cannot determine the accurate volume of ovary. Based on our studies, we suggest that 3D ultrasound is more appropriate than conventional 2D ultrasound in assessing the ultrasound criteria of PCOS.

Ovulation Induction

3D ultrasound can accurately measure the true volume of ovarian follicles in follicular development of assisted controlled ovarian stimulation cycles. It can also accurately demonstrate the largest dimensions of the follicles, which is critical for the timing of human chorionic gonadotrophin (hCG) injection. We used the 3D power Doppler ultrasonographic indices to quantify ovarian stromal blood flow and vascularization in hyperresponders and poor responders [14,15]. A hyperresponder group (peak estradiol $>$ 3,000 pg/mL; or $\geq$ 15 oocytes retrieved) and poor responder group (estradiol $<$ 600 pg/mL; or $\leq$ 3 oocytes retrieved) undergoing an *in vitro* fertilization (IVF) cycle were defined based on their response to a standard downregulation protocol for controlled ovarian stimulation. The VFI, FI, and VI were significantly higher in the hyperresponders (1.18 $\pm$ 0.60, 50.23 $\pm$ 2.81, and 2.27 $\pm$ 1.08, respectively), compared with the women with a normal response (0.63 $\pm$ 0.61, 43.19 $\pm$ 7.81, and 1.25 $\pm$ 1.18, respectively) in the hyperresponder study [14]. The VI, FI, and VFI were significantly lower in the poor responder group (0.13 $\pm$ 0.11, 30.89 $\pm$ 10.35, and 0.05 $\pm$ 0.04, respectively), compared with the women with a normal response (1.20 $\pm$ 1.10, 43.88 $\pm$ 7.77, and 0.61 $\pm$ 0.57, respectively) [15]. Therefore, our studies using 3D power Doppler indices of ovarian stromal blood flow may help to explain the excessive and poor responses during gonadotropin administration in controlled ovarian stimulation.

Successful implantation and pregnancy depend on the quality of embryo and endometrial receptivity. In the medical literature, various parameters are used to evaluate endometrial receptivity. Using 3D color Doppler, the blood supply and volume in the entire endometrium and the subendometrial regions can be evaluated deliberatively. Although the subendometrial vascularization and flow indices were low in women with poor uterine blood flow indices, Ng and co-workers demonstrated that the uterine Doppler blood flow cannot reflect the endometrial and subendometrial environment accurately [19]. Jarvela and co-workers showed that there were no significant differences in endometrial thickness, volume, and flow during IVF between pregnant women and nonpregnant women using 3D power Doppler ultrasonography [20]. The endometrial and subendometrial vascularity decreased after hCG injection in both groups. Only endometrial volume decreased significantly after hCG injection in the conception group. In addition, the values of endometrial and subendometrial vascularity in women who conceived, leading to live birth, were significantly higher than those of women who suffered miscarriage following IVF treatment [21]. However, these data indicate that the use of 3D ultrasonography to evaluate IVF outcome is still controversial; further studies are warranted.

Endometriosis

One of our studies on PCOS and IVF demonstrated significantly lower indices of intraovarian blood flow in endometriosis patients during IVF, with the use of 3D power Doppler ultrasound analysis [12]. The ovaries from patients with endometriosis showed lower VI, FI and VFI values than the tubal factor group (VI, 0.72 $\pm$ 0.20 *vs*. 1.69 $\pm$ 0.60; FI, 41.88 $\pm$ 1.83 *vs*. 45.84 $\pm$ 1.32; *vs*. VFI, 0.35 $\pm$ 0.10 *vs*. 0.91 $\pm$ 0.35; respectively). The decreased ovarian vascularity in the endometriosis group may be due to ovarian damage during operation.

However, there was no significant difference in stromal blood flow parameters between the endometriomatous ovaries and the control ovaries using 3D power Doppler ultrasound. Because the deficiency of intraovarian vascularity may potentially be an initial marker of reduced ovarian reserve before the increase of follicle-stimulating hormone level and the reduction of ovarian volume, our results are compatible with the decreased ovarian stroma FI and lower pregnancy rate without the evident changes in baseline follicle-stimulating hormone level and ovarian volume after gonadotropin stimulation were noted in the endometriosis group. Leptin is considered as an angiogenic factor, and the follicular fluid (FF) leptin is a marker of "follicular hypoxia". Follicular hypoxia secondary to reduced blood flow (decreased FI) in ovarian stroma may induce the secretion of several angiogenic factors, such as leptin, in ovarian follicles. In our study, there was a negative correlation between the FF leptin levels (or FF leptin/BMI) and the power Doppler FI in control group. It is interesting that loss of this negative correlation between FF leptin and FI was noted in the endometriosis group, which may imply deficient angiogenic responses in ovarian cortices after operative treatment for endometriosis.

Recently, endoscopic ultrasound has become a useful technique for colon and rectal disease, including for the imaging and intervention of rectosigmoid involvement by endometriosis [22]. It helps to detect any lesions of endometriosis in the rectovaginal septum and the degree in the infiltration of the rectal wall but is less effective for endometriotic nodules in the uterosacral ligaments and ovaries. The role of 3D ultrasonography may be studied to evaluate the condition before surgical exploration or the correlation with patient's clinical course of endometriosis.

Aging and Menopause

During the last decade, we first used the 3D power Doppler ultrasonography to test the hypothesis that the flow intensity of the ovarian stroma decreases during the aging process and proved that the flow intensity decreases along with the aging process in the ovarian stroma [11]. The VI (6.95 ± 8.35; 1.11 ± 0.93; 0.53 ± 1.75; respectively), FI (15.98 ± 7.59; 12.00 ± 3.86; 5.18 ± 5.31; respectively) and VFI (1.25 ± 1.59; 0.18 ± 0.15; 0.09 ± 0.32; respectively) all decreased significantly in the order of pre-menopause, peri-menopause, then post-menopause, which were compatible with the decreased values of estrogens. In contrast, there was a significant increase in ovarian stromal flow indices after 3 months of continuous–combined hormone replacement therapy, but not in control patients [13]. All of the 3D power Doppler indices of ovarian stromal flow, VFI (0.13 ± 0.11 *vs.* 0.59 ± 0.49), FI (30.47 ± 12.06 *vs.* 38.41 ± 10.21) and VI (0.31 ± 0.27 *vs.* 1.12 ± 0.95), showed significant increase after treatment. Monitoring the ovarian flow changes by 3D power Doppler may be of clinical importance during hormone therapy in menopause. 3D power Doppler ultrasound can be performed to evaluate ovarian morphology and microcirculation anatomy of the ovarian lesions at the same time. In spite of low incidence of ovarian cancer, annual 3D power Doppler ultrasonography can help to detect this disease early and accurately in high-risk asymptomatic peri- and postmenopausal women [23].

In postmenopausal bleeding, Gruboeck and coworkers reported that the cutoff level of 13 mL of 3D endometrium volume measurement with a sensitivity of 100% and a positive predictive value of 91.7% was better than 2D endometrial thickness measurement in the diagnosis of endometrial cancer [24]. Yaman and coworkers also demonstrated that the reproducibility of endometrial volume measurement with transvaginal 3D ultrasound was superior to that of endometrial thickness measurement with 2D ultrasound. 3D ultrasound volume measurement may easily illustrate the frequently asymmetric endometrium outline and thus improve the accuracy in diagnosis and assist in the management of diseases in postmenopausal women [25].

Congenital Müllerian Duct Anomalies

One of the most impressive clinical applications of 3D transvaginal ultrasound is the detection of congenital müllerian duct anomalies. Many diagnostic methods are used to evaluate uterine morphologic anomalies, including hysterosalpingography, laparoscopy, hysteroscopy, traditional 2D ultrasound, and nuclear magnetic resonance. In addition, 3D ultrasound can demonstrate both endometrial cavity and fundal myometrial contour, which help to differentiate different types of müllerian duct malformations in patients with histories of repeated spontaneous abortions or infertility [3]. High sensitivity, specificity, positive predictive value, and negative predictive value of 3D sonography for detecting müllerian duct anomalies are well documented. Salim and co-workers further confirmed that 3D ultrasound was a good reproducible method with reasonable inter- and intraobserver variabilities in the measurement and diagnosis of müllerian duct anomalies [26]. Therefore, 3D ultrasound provides more comprehensive images of both uterine cavity configuration and adnexal structure, especially after 3D rendering, than does traditional 2D sonography, and facilitates the differential diagnosis of septate from bicornuate uteri for preoperative surgical planning.

It is relatively difficult to detect other rare types of müllerian duct anomalies, such as unilateral occlusion of duplicated uterus with ipsilateral renal anomaly, early in adolescence. Traditional 2D ultrasound study may only illustrate pelvic lesions but fails to recognize the defined disease entity. With 3D sonography, we can demonstrate these rare congenital anatomic relationships and provide optimal management [4]. Early application of 3D sonography in young girls suspected of having the anomalies can avoid unnecessary examinations and invasive interventions and can help decrease the morbidity and improve their quality of life. Congenital cervical atresia is another rare anomaly caused by abnormal development of the müllerian system. We demonstrated that assisted reproductive technologies may offer a better opportunity to achieve pregnancy in patients with complete or partial cervical atresia with the help of 3D ultrasound [27]. In addition, 3D ultrasound can help distinguish different types of uterine anomalies. In a pilot study using 3D power Doppler ultrasonography, we observed a decreased amount of uterine blood flow without change in vessel number after surgery for bicornuate uterus; further evaluation is being undertaken now at our unit.

Intrauterine Lesions

3D ultrasound can detect not only uterine anatomy but also intrauterine pathology. 3D ultrasound facilitates the display of arbitrary planes of the uterus, which are sometimes undetectable by traditional 2D ultrasound because of unsuitable position. At present, we can straightforwardly demonstrate the position, shape, and size of the foreign body such as intrauterine device or retained fetal bones, especially after 3D image reconstruction, and thus aid in the preoperative assessment by hysteroscopy [5]. Furthermore, 3D sonohysterography, which involves the distension of the uterine cavity with saline, can accurately appraise intrauterine lesions, especially in the classification of submucous myoma when compared with diagnostic hysteroscopy [28]. We have described a case of uterine arteriovenous malformations after dilatation and curettage diagnosed with the aid of 3D power Doppler ultrasonography [6]. The diagnosis of arteriovenous malformations after dilatation and curettage is difficult, and usually, radioactive angiography has to be undertaken to reach this diagnosis. Using 3D power Doppler ultrasound, which is simple and nonradioactive, we can repeatedly identify and quantify its vascularization and blood flow and observe the VI, VFI and the region of interest gradually decrease during the follow-up period. However, the FI remained similar to its initial value. Obviously, 3D power Doppler is simpler, cheaper, and more convenient, noninvasive and nonradioactive than radioactive angiography. Therefore, 3D power Doppler angiography may be considered as an alternative tool for primary diagnosis and monitoring of the uterine arteriovenous malformations.

Conclusion

Over the past decade, we have investigated the clinical application of 3D ultrasound in many fields of obstetrics and gynecology. 3D ultrasound with rendering mode is a safe and noninvasive technique in the assessment of internal genital organs. Clearly, 3D ultrasound provides several advantages beyond those of conventional 2D scanning. The rendered imaging of 3D ultrasound allows physicians to comprehend and evaluate the sophisticated anatomy of the female pelvis with ease by observing from any arbitrary planes. However, 3D ultrasound still requires more experience in training and operating than 2D ultrasound. 3D ultrasound is not perfect; there are many technical problems of 3D ultrasound yet to be solved currently. From our studies, 3D power Doppler ultrasound may be an important tool to provide substantial assistance in future clinical application and management. Further research should be conducted to explore more potential uses of 3D and power Doppler ultrasonography in the investigation of infertility and reproductive endocrinology.

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